

Search Plan and Results

Question

What impact has mandatory folic acid fortification had on the incidence of neural tube defect in the US and Canada? (DGAC 2010)

What effect has folic acid fortification policy had on serum folate, plasma and red blood cell folate status of US Canada women, men and children? (DGAC 2010)

Date Searched

5-27-2009

Inclusion Criteria

- *Subjects/Population:* Human subjects
- *Age:* Men, women, and children
- *Setting:* US and Canada only
- *Health status:* Healthy and those with elevated chronic disease risk (CHD/CVD, type 2 diabetes, metabolic syndrome and obesity)
- *Nutrition related problem/Condition:* None.

Search Criteria

- *Study design preferences:* RCT or clinical controlled studies, large non-randomized observational studies, cohort and systematic reviews
- *Size of study groups:* The sample size must equal 10 adults for each study group. For example, this would include 10 patients in the intervention group and 10 patients in the control or comparison group
- *Study dropout rate:* Less than 20%; preference for smaller dropout rates
- *Year range:* June 1999 to present
- *Authorship:* If an author is included on more than one review article or primary research article that is similar in content, the most recent review or article will be accepted and earlier versions will be rejected
- *Languages:* Limited to articles in English
- *Other:* Article must be published in peer-reviewed journal.

Exclusion Criteria

- *Subjects/Population:* Populations outside the U.S. and Canada
- *Setting:* Hospitalized patients
- *Health status:* Medical treatment or therapy and diseased subjects (already diagnosed with disease related to study purpose).

Search Criteria

- *Size of study groups:* Sample sizes less than 10

- *Study dropout rate*: Dropout rate in a study of 20% or greater
- *Year range*: Prior to June 1999
- *Authorship*: Studies by same author similar in content
- *Languages*: Articles not in English
- *Other*: Abstracts or presentations and articles not peer reviewed (websites, magazine articles, Federal reports, etc.).

Search Terms: Search Vocabulary

Comparators

- Intake levels/consumption levels
- Fortification
- Supplementation.

Health Outcomes/Clinical Disease

NTD.

Other Terms

NHANES.

Electronic Databases

Database

PubMed.

Search Terms

("Neural Tube Defects"[Mesh] OR NTDs[All Fields] OR "Spinal Dysraphism"[Mesh] or "Anencephaly"[Mesh]) AND ("Folic Acid"[Mesh] OR ("folic acid"[MeSH Terms] OR ("folic"[All Fields] AND "acid"[All Fields])) OR "folic acid"[All Fields] OR "folate"[All Fields])) AND "English and humans"[Filter] Limits: published in the last 10 years. ("Folic Acid"[majr] OR folate) AND (fortification OR "Food, Fortified"[Mesh]) AND (serum OR plasma OR "red blood cell*" OR RBC*) AND ("Canada"[Mesh] OR "United States"[Mesh]) Limits: published in the last 10 years.

Total hits from all electronic database searches: 1099

Total articles identified to review from electronic databases: 82

Articles Identified Via Handsearch or Other Means

Hand-search articles: 2 (05/05/2009).

Summary of Articles Identified to Review

Number of Primary Articles Identified: 24

Number of Review Articles Identified: 0

Total Number of Articles Identified: 24

Number of Articles Reviewed but Excluded: 60

List of Articles Included for Evidence Analysis

What Effect Does Folic Acid Fortification Policy Have on Serum, Plasma and Red Blood Cell Folate Status of US and Canadian Men, Women and Children?

Bar-Oz B, Koren G, Nguyen P, Kapur BM. [Folate fortification and supplementation: Are we there yet? Reprod Toxicol.](#) 2008 Aug; 25(4): 408-412. Epub 2008 May 3. PMID: 18550330.

Dietric M, Brown CJ, Block G. [The effect of folate fortification of cereal-grain products on blood folate status, dietary folate intake, and dietary folate sources among adult non-supplement users in the United States. J Am Coll Nutr.](#) 2005 Aug; 24(4): 266-274. PMID: 16093404.

Dowd JB, Aiello AE. [Did national folic acid fortification reduce socioeconomic and racial disparities in folate status in the US? Int J Epidemiol.](#) 2008 Oct; 37(5): 1, 059-1, 066. Epub 2008 May 2. PMID: 18456713.

Felkner M, Suarez L, Hendricks K, Gunter EW. [Blood folate levels on the Texas-Mexico border.](#)

Tex Med. 2002 Nov; 98(11): 58-60. PMID: 12448957.

Ganji V, Kafai MR. [Trends in serum folate, RBC folate, and circulating total homocysteine concentrations in the United States: Analysis of data from National Health and Nutrition Examination Surveys, 1988-1994, 1999-2000, and 2001-2002. J Nutr.](#) 2006 Jan; 136(1): 153-158. PMID: 16365075.

Jacques PF, Selhub J, Boston AG, Wilson PW, Rosenberg IH. [The effect of folic acid fortification on plasma folate and total homocysteine concentrations. N Engl J Med.](#) 1999 May 13; 340(19): 1, 449-1, 454. PMID: 10320382 (HS).

Kalmbach RD, Choumenkovitch SF, Troen AM, D'Agostino R, Jacques PF, Selhub J.

[Circulating folic acid in plasma: Relation to folic acid fortification.](#) *Am J Clin Nutr.* 2008 Sep; 88(3): 763-768. PMID: 18779294.

Pfeiffer CM, Johnson CL, Jain RB, Yetley EA, Picciano MF, Rader JI, Fisher KD, Mulinare J, Osterloh JD. [Trends in blood folate and vitamin B-12 concentrations in the United States, 1988-2004.](#) *Am J Clin Nutr.* 2007 Sep; 86(3): 718-727. PMID: 17823438.

[Quinlivan EP, Gregory JF 3rd. Reassessing folic acid consumption patterns in the United States \(1999-2004\): Potential effect on neural tube defects and overexposure to folate.](#) *Am J Clin Nutr.* 2007 Dec; 86(6): 1773-9. PMID: 18065598.

Ray JG, Vermeulen MJ, Boss SC, Cole DE. [Declining rate of folate insufficiency among adults following increased folic acid food fortification in Canada.](#) *J Public Health.* 2002 Jul-Aug; 93(4): 249-253. PMID: 12154524.

Shuaibi AM, House JD, Sevenhuijsen GP. [Folate status of young Canadian women after folic acid fortification of grain products.](#) *J Am Diet Assoc.* 2008 Dec; 108(12): 2, 090-2, 094. PMID: 19027414.

What Impact has Mandatory Folic Acid Fortification had on the Incidence of Neural Tube Defect in the U.S. and Canada?

Besser LM, Williams LJ, Cragan JD. [Interpreting changes in the epidemiology of anencephaly and spina bifida following folic acid fortification of the U.S. grain supply in the setting of long-term trends, Atlanta, Georgia, 1968-2003.](#) *Birth Defects Res A Clin Mol Teratol.* 2007 Nov; 79(11): 730-736. PMID: 17990332.

Canfield MA, Collins JS, Botto LD, Williams LJ, Mai CT, Kirby RS, Pearson K, Devine O, Mulinare J; National Birth Defects Prevention Network. [Changes in the birth prevalence of selected birth defects after grain fortification with folic acid in the United States: Findings from a multi-state population-based study.](#) *Birth Defects Res A Clin Mol Teratol.* 2005 Oct; 73(10): 679-689. PMID: 16240378.

Centers for Disease Control and Prevention (CDC). [Spina bifida and anencephaly before and after folic acid mandate: United States, 1995-1996 and 1999-2000.](#) *MMWR Morb Mortal Wkly Rep.* 2004 May 7; 53(17): 362-365. PMID: 15129193.

Chen BH, Carmichael SL, Selvin S, Abrams B, Shaw GM. [NTD prevalences in central California before and after folic acid fortification.](#) *Birth Defects Res A Clin Mol Teratol.* 2008 Aug; 82(8): 547-552. PMID: 18496833.

De Wals P, Tairou F, Van Allen MI, Lowry RB, Evans JA, Van den Hof MC, Crowley M, Uh SH, Zimmer P, Sibbald B, Fernandez B, Lee NS, Niyonsenga T. [Spina bifida before and after folic acid fortification in Canada.](#) *Birth Defects Res A Clin Mol Teratol.* 2008 Sep; 82(9): 622-626. PMID: 18655127.

De Wals P, Tairou F, Van Allen MI, Uh SH, Lowry RB, Sibbald B, Evans JA, Van den Hof MC, Zimmer P, Crowley M, Fernandez B, Lee NS, Niyonsenga T. [Reduction in neural-tube defects after folic acid fortification in Canada.](#) *N Engl J Med.* 2007 Jul 12; 357(2): 135-142. PMID: 17625125.

Forrester MB, Merz RD. [Rates of selected birth defects in relation to folic acid fortification, Hawaii, 1986-2002.](#) *Hawaii Med J.* 2005 Dec; 64(12): 300, 302-305. PMID: 16438020.

Godwin KA, Sibbald B, Bedard T, Kuzeljevic B, Lowry RB, Arbour L. [Changes in frequencies of select congenital anomalies since the onset of folic acid fortification in a Canadian birth defect registry](#). *Can J Public Health*. 2008 Jul-Aug; 99(4): 271-275. PMID: 18767269.

Honein MA, Paulozzi LJ, Mathews TJ, Erickson JD, Wong LY. [Impact of folic acid fortification of the US food supply on the occurrence of neural tube defects](#). *JAMA*. 2001 Jun 20; 285(23): 2, 981-2, 986. Erratum in: *JAMA*. 2001 Nov 14; 286(18): 2, 236. PMID: 11410096.

Mosley BS, Hobbs CA, Flowers BS, Smith V, Robbins JM. [Folic acid and the decline in neural tube defects in Arkansas](#). *J Ark Med Soc*. 2007 Apr; 103(10): 247-250. PMID: 17487022.

Persad VL, Van den Hof MC, Dubé JM, Zimmer P. [Incidence of open neural tube defects in Nova Scotia after folic acid fortification](#). *CMAJ*. 2002 Aug 6; 167(3): 241-245. PMID: 12186168 (HS).

Williams LJ, Rasmussen SA, Flores A, Kirby RS, Edmonds LD. [Decline in the prevalence of spina bifida and anencephaly by race/ethnicity: 1995-2002](#). *Pediatrics*. 2005 Sep; 116(3): 580-586. PMID: 16140696.

Williams LJ, Mai CT, Edmonds LD, Shaw GM, Kirby RS, Hobbs CA, Sever LE, Miller LA, Meaney FJ, Levitt M. [Prevalence of spina bifida and anencephaly during the transition to mandatory folic acid fortification in the United States](#). *Teratology*. 2002 Jul; 66(1): 33-39. PMID: 12115778.

List of Excluded Articles with Reason

Excluded Articles (A-G)	Reason for Exclusion
Antoniades C, Antonopoulos AS, Tousoulis D, Marinou K, Stefanidis C. Homocysteine and coronary atherosclerosis: From folate fortification to the recent clinical trials. www.ncbi.nlm.nih.gov/pubmed/19029125 <i>Eur Heart J</i> . 2009 Jan; 30(1): 6-15. Epub 2008 Nov 23. Review. PMID: 19029125.	Does not answer the question; about homocysteine and CVD.
Bleys J, Miller ER 3rd, Pastor-Barriuso R, Appel LJ, Guallar E. Vitamin-mineral supplementation and the progression of atherosclerosis: a meta-analysis of randomized controlled trials. www.ncbi.nlm.nih.gov/pubmed/17023716 <i>Am J Clin Nutr</i> . 2006 Oct; 84(4): 880-887; quiz 954-955. PMID: 17023716.	Does not answer the question; about antioxidants and B vitamins.
Bor MV, Wulff AM, Nexo E, Krarup H. Clin Chem Infrequency of low red blood cell (RBC) folate levels despite no folate fortification program: a study based on results from routine requests for RBC folate . <i>Lab Med</i> . 2008; 46(3): 401-404. PMID: 18254711.	International study.

<p>Boston AG, Jacques PF, Liaugaudas G, Rogers G, Rosenberg IH, Selhub J. Total homocysteine lowering treatment among coronary artery disease patients in the era of folic acid-fortified cereal grain flour. www.ncbi.nlm.nih.gov/pubmed/11884295 <i>Arterioscler Thromb Vasc Biol.</i> 2002 Mar 1; 22(3): 488-491. PMID: 11884295.</p>	<p>Does not answer the question; about homocysteine.</p>
<p>Botto LD, Lisi A, Bower C, Canfield MA, Dattani N, De Vigan C, De Walle H, Erickson DJ, Halliday J, Irgens LM, Lowry RB, McDonnell R, Metneki J, Poetzsch S, Ritvanen A, Robert-Gnansia E, Siffel C, Stoll C, Mastroiacovo P. Trends of selected malformations in relation to folic acid recommendations and fortification: An international assessment. <i>Birth Defects Res A Clin Mol Teratol.</i> 2006 Oct; 76(10): 693-705. PMID: 17029289.</p>	<p>International article.</p>
<p>Boulet SL, Yang Q, Mai C, Kirby RS, Collins JS, Robbins JM, Meyer R, Canfield MA, Mulinare J; National Birth Defects Prevention Network. Trends in the postfortification prevalence of spina bifida and anencephaly in the United States. <i>Birth Defects Res A Clin Mol Teratol.</i> 2008 Jul; 82(7): 527-532. PMID: 18481813.</p>	<p>Does not answer the question; evaluated only post-fortification.</p>
<p>Boushey CJ, Edmonds JW, Welshimer KJ. Estimates of the effects of folic-acid fortification and folic-acid bioavailability for women. <i>Nutrition.</i> 2001 Oct; 17(10): 873-879. PMID: 11684395.</p>	<p>Does not answer the research question</p>
<p>Byrne J, Carolan S, Arcement R, Kozlowski M, Taller I, Ried S, Keating R. An intervention study to increase knowledge and use of folic acid among relatives in neural tube defect-affected families in Washington, D.C. <i>Birth Defects Res A Clin Mol Teratol.</i> 2005 Jun; 73(6): 424-429. PMID: 15880789.</p>	<p>Does not answer the question; about knowledge and intake.</p>
<p>Canfield MA, Anderson JL, Waller DK, Palmer SE, Kaye CI. Folic acid awareness and use among women with a history of a neural tube defect pregnancy: Texas, 2000-2001. <i>MMWR Recomm Rep.</i> 2002 Sep 13; 51(RR-13): 16-19. PMID: 12353508.</p>	<p>Population with recurrent NTD.</p>
<p>Carlsson CM. Homocysteine lowering with folic acid and vitamin B supplements: effects on cardiovascular disease in older adults. www.ncbi.nlm.nih.gov/pubmed/16872232 <i>Drugs Aging.</i> 2006; 23(6): 491-502. Review. PMID: 16872232.</p>	<p>It doesn't answer the question. About B supplements and cardiovascular protection.</p>
<p>Caudill MA, Le T, Moonie SA, Esfahani ST, Cogger EA. Folate status in women of childbearing age residing in Southern California after folic acid fortification. <i>J Am Coll Nutr.</i> 2001 Apr; 20(2 Suppl): 129-134. Erratum in: <i>J Am Coll Nutr.</i> 2001 Jun; 20(3): 268. PMID: 11349935.</p>	<p>Does not answer the research question.</p>

<p>CDC, MMWR Weekly report, 2002. Folate Status in Women of Childbearing Age, by Race/Ethnicity: United States, 1999-2000. September 13, 2002; 51(36): 808-810.</p> <p>http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5136a2.htm</p>	<p>Data used in this article was analyzed in the Quilivan et al., 2007 article, which was included.</p>
<p>CDC, MMWR Weekly report, 2009. Folate Status in Women of Childbearing Age, by Race/Ethnicity: United States, 1999-2000, 2001-2002 and 2003-2004. January 5, 2007; 55(51):1, 377-1, 380.</p> <p>http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5551a2.htm</p>	<p>Data used in this article was analyzed in the Quilivan et al., 2007 study, which was included.</p>
<p>Cena ER, Joy AB, Heneman K, Espinosa-Hall G, Garcia L, Schneider C, Wooten Swanson PC, Hudes M, Zidenberg-Cherr S. <u>Folate intake and food-related behaviors in nonpregnant, low-income women of childbearing age.</u> <i>J Am Diet Assoc.</i> 2008 Aug; 108(8): 1, 364-1, 368. PMID: 18656578.</p>	<p>Does not answer the research question.</p>
<p>Clarke R, Collins R. Can dietary supplements with folic acid or vitamin B₆ reduce cardiovascular risk? Design of clinical trials to test the homocysteine hypothesis of vascular disease.</p> <p>www.ncbi.nlm.nih.gov/pubmed/9919473 <i>J Cardiovasc Risk.</i> 1998 Aug; 5(4): 249-255. PMID: 9919473.</p>	<p>Not a systematic review.</p>
<p>Choumenkovitch SF, Selhub J, Wilson PW, Rader JI, Rosenberg IH, Jacques PF. <u>Folic acid intake from fortification in United States exceeds predictions</u> <i>J Nutr.</i> 2002 Sep; 132(9): 2, 792-2, 798. PMID: 12221247</p>	<p>Does not answer the research question.</p>
<p>Cornel MC, de Smit DJ, de Jong-van den Berg LT. <u>Folic acid: The scientific debate as a base for public health policy.</u> <i>Reprod Toxicol.</i> 2005 Sep-Oct; 20(3): 411-415. Review. PMID: 15978774.</p>	<p>Commentary.</p>
<p>De Bree A, Mennen LI, Hercberg S, Galan P. Evidence for a protective (synergistic?) effect of B-vitamins and omega-3 fatty acids on cardiovascular diseases.</p> <p>www.ncbi.nlm.nih.gov/pubmed/15116076 <i>Eur J Clin Nutr.</i> 2004 May; 58(5): 732-744. PMID: 15116076.</p>	<p>Does not answer the question.</p>
<p>de Jong-Van den Berg LT, Hernandez-Diaz S, Werler MM, Louik C, Mitchell AA. <u>Trends and predictors of folic acid awareness and periconceptional use in pregnant women.</u> <i>Am J Obstet Gynecol.</i> 2005 Jan; 192(1): 121-128. PMID: 15672013.</p>	<p>Does not answer the question; about awareness.</p>
<p>DeWolfe J, Can J. <u>Folate intake of older adults before and after fortification of grain products.</u> <i>Diet Pract Res.</i> 2007 Winter; 68(4): 218-220. PMID: 18073005.</p>	<p>Measure intake not RBC or plasma folate.</p>

<p>Evans MI, Llurba E, Landsberger EJ, O'Brien JE, Harrison HH. <u>Impact of folic acid fortification in the United States: Markedly diminished high maternal serum alpha-fetoprotein values.</u> <i>Obstet Gynecol.</i> 2004 Mar; 103(3): 474-479. PMID: 14990409.</p>	<p>Does not answer the question; addresses alpha-fetoprotein values.</p>
<p>Goh YI, Bollano E, Einarson TR, Koren G. Prenatal multivitamin supplementation and rates of congenital anomalies: A meta-analysis. <u>www.ncbi.nlm.nih.gov/pubmed/17022907</u> <i>J Obstet Gynaecol Can.</i> 2006 Aug; 28(8): 680-689. Review. PMID: 17022907.</p>	<p>Folic acid intake is not quantified.</p>
<p>Grosse SD, Collins JS. <u>Folic acid supplementation and neural tube defect recurrence prevention.</u> <i>Birth Defects Res A Clin Mol Teratol.</i> 2007 Nov; 79(11): 737-742. PMID: 17990333.</p>	<p>Does not answer the question; about recurrence.</p>

Excluded Articles (K-R)	Reason for Exclusion
<p>Kannan S, Menotti E, Scherer HK, Dickinson J, Larson K. <u>Folic acid and the prevention of neural tube defects: A survey of awareness among Latina women of childbearing age residing in southeast Michigan.</u> <i>Health Promot Pract.</i> 2007 Jan; 8(1): 60-68. Epub 2006 Jul 13. PMID: 16840767.</p>	<p>Does not answer the question; about awareness.</p>
<p>Klerk M, Durga J, Schouten EG, Kluft C, Kok FJ, Verhoef P. No effect of folic acid supplementation in the course of one year on haemostasis markers and C-reactive protein in older adults. <u>www.ncbi.nlm.nih.gov/pubmed/16113791</u> <i>Thromb Haemost.</i> 2005 Jul; 94(1): 96-100. PMID: 16113791.</p>	<p>Does not answer the question; about supplementation and homocysteine.</p>
<p>Lambert-Messerlian G, Halliday J, Williams J, Cain R, Msall ME, Palomaki GE, Canick JA. <u>Effect of folic acid fortification on prevalence of neural tube defects in Rhode Island.</u> <i>J Med Screen.</i> 2004; 11(2): 106-107. PMID: 15153328.</p>	<p>Letter to the editor.</p>
<p>Lewis SJ, Ebrahim S, Davey Smith G. Meta-analysis of MTHFR 677C-T polymorphism and coronary heart disease: Does totality of evidence support causal role for homocysteine and preventive potential of folate? <u>www.ncbi.nlm.nih.gov/pubmed/16216822</u> <i>BMJ.</i> 2005 Nov 5; 33 1(7, 524): 1, 053. Epub 2005 Oct 10. Review. PMID: 16216822.</p>	<p>Not a systematic review; does not answer the question; about genotype.</p>
<p>Lumley J, Watson L, Watson M, Bower C. Cochrane <u>Periconceptional supplementation with folate and/or multivitamins for preventing neural tube defects.</u> <i>Database Syst Rev.</i> 2001;(3): CD001056. Review. PMID: 11686974.</p>	<p>Does not answer the question; about NTD and supplementation.</p>

<p>Malinow MR, Duell PB, Irvin-Jones A, Upson BM, Graf EE. Increased plasma homocyst(e)ine after withdrawal of ready-to-eat breakfast cereal from the diet: Prevention by breakfast cereal providing 200 microg folic acid. www.ncbi.nlm.nih.gov/pubmed/10963464 <i>J Am Coll Nutr.</i> 2000 Aug; 19(4): 452-457. PMID: 10963464.</p>	<p>Does not answer the question; about homocysteine.</p>
<p>Mark L, Erdei F, Markizay J, Kondacs A, Katona A. Effect of treatment with folic acid and vitamin B₆ on lipid and homocysteine concentrations in patients with coronary artery disease. www.ncbi.nlm.nih.gov/pubmed/11985950 <i>Nutrition.</i> 2002 May; 18(5): 428-429. No abstract available. PMID: 11985950.</p>	<p>Does not answer the question; about supplementation and homocysteine.</p>
<p>McCully KS. Homocysteine, vitamins, and vascular disease prevention. www.ncbi.nlm.nih.gov/pubmed/17991676 <i>Am J Clin Nutr.</i> 2007 Nov; 86(5): 1, 563S-1, 568S. Review. PMID: 17991676.</p>	<p>Does not answer the question; about homocysteine.</p>
<p>McEligot AJ, Rock CL, Gilpin EA, Pierce JP. Responsiveness of homocysteine concentrations to food and supplemental folate intakes in smokers and never-smokers enrolled in a diet intervention trial. www.ncbi.nlm.nih.gov/pubmed/16497600 <i>Nicotine Tob Res.</i> 2006 Feb; 8(1): 57-66. PMID: 16497600.</p>	<p>Does not answer the question; about homocysteine.</p>
<p>McKay DL, Perrone G, Rasmussen H, Dallal G, Blumberg JB. Multivitamin/mineral supplementation improves plasma B-vitamin status and homocysteine concentration in healthy older adults consuming a folate-fortified diet. www.ncbi.nlm.nih.gov/pubmed/11110875</p>	<p>Does not answer the question; about supplementation and homocysteine.</p>
<p>Mills JL, Signore C. Neural tube defect rates before and after food fortification with folic acid. <i>Birth Defects Res A Clin Mol Teratol.</i> 2004 Nov; 70(11): 844-845. Review. PMID: 15468072</p>	<p>Review of four articles; three primary articles were included.</p>
<p>Moats C, Rimm EB. Vitamin intake and risk of coronary disease: observation versus intervention. <i>Curr Atheroscler Rep.</i> 2007 Dec; 9(6): 508-514. Review. www.ncbi.nlm.nih.gov/pubmed/18377792 PMID: 18377792</p>	<p>Not a systematic review; does not answer the question.</p>
<p>Mosley BS, Cleves MA, Siega-Riz AM, Shaw GM, Canfield MA, Waller DK, Werler MM, Hobbs CA; National Birth Defects Prevention Study. Neural tube defects and maternal folic acid intake among pregnancies conceived after folic acid fortification in the United States. <i>Am J Epidemiol.</i> 2009 Jan 1; 169(1): 9-17. Epub 2008 Oct 25. PMID: 18953063.</p>	<p>Does not address the question; evaluated the relation of NTD and maternal folic acid consumption after folic acid fortification.</p>

<p>Muskiet FA. The importance of (early) folate status to primary and secondary coronary artery disease prevention. www.ncbi.nlm.nih.gov/pubmed/15964170 <i>Reprod Toxicol.</i> 2005 Sep-Oct; 20(3): 403-410. Review. PMID: 15964170.</p>	<p>Not a systematic review.</p>
<p>Ntaios GC, Savopoulos CG, Chatzinikolaou AC, Kaifa GD, Hatzitolios A. Vitamins and stroke: The homocysteine hypothesis still in doubt. <i>Neurologist.</i> 2008 Jan; 14(1): 2-4. Review. www.ncbi.nlm.nih.gov/pubmed/18195649 PMID: 18195649.</p>	<p>Not a systematic review; about vitamins and CVD.</p>
<p>Palomaki GE, Williams J, Haddow JE. Comparing the observed and predicted effectiveness of folic acid fortification in preventing neural tube defects. <i>J Med Screen.</i> 2003; 10(1): 52-53. PMID: 12790316.</p>	<p>Letter to the editor.</p>
<p>Quinlivan EP, McPartlin J, McNulty H, Ward M, Strain JJ, Weir DG, Scott JM. Importance of both folic acid and vitamin B₁₂ in reduction of risk of vascular disease. <i>Lancet.</i> 2002 Jan 19; 359(9, 302): 227-228. PMID: 11812560.</p>	<p>Does not answer the question; about homocysteine.</p>
<p>Rader JI, Schneeman BO. Prevalence of neural tube defects, folate status, and folate fortification of enriched cereal-grain products in the United States. <i>Pediatrics.</i> 2006 Apr; 117(4): 1, 394-1, 399. PMID: 16585338.</p>	<p>Not a systematic review.</p>
<p>Ramos MI, Allen LH, Mungas DM, Jagust WJ, Haan MN, Green R, Miller JW. Low folate status is associated with impaired cognitive function and dementia in the Sacramento Area Latino Study on Aging. <i>Am J Clin Nutr.</i> 2005 Dec; 82(6): 1, 346-1, 352. PMID: 16332669.</p>	<p>Does not answer the question; about dementia and folate status.</p>
<p>Ray JG, Vermeulen MJ, Boss SC, Cole DE. Declining rate of folate insufficiency among adults following increased folic acid food fortification in Canada. <i>Can J Public Health.</i> 2002 Jul-Aug; 93(4): 249-253. PMID: 12154524.</p>	<p>Does not address the question; investigates the changes in folate and vitamin B₁₂ insufficiency after folic acid fortification.</p>
<p>Rydlewicz A, Simpson JA, Taylor RJ, Bond CM, Golden MH. The effect of folic acid supplementation on plasma homocysteine in an elderly population. <i>QJM.</i> 2002 Jan; 95(1): 27-35. PMID: 11834770.</p>	<p>Does not answer the question; about supplementation and homocysteine.</p>

Excluded Articles (S to Z)

Reason for Exclusion

<p>Sauer J, Mason JB, Choi SW. Too much folate: A risk factor for cancer and cardiovascular disease? www.ncbi.nlm.nih.gov/pubmed/19057184 <i>Curr Opin Clin Nutr Metab Care.</i> 2009 Jan; 12(1): 30-36. Review. PMID: 19057184.</p>	<p>Not a systematic review.</p>
<p>Smolková B, Dusinská M, Raslová K, Barancoková M, Kazimírová A, Horská A, Spustová V, Collins A. Folate levels determine effect of antioxidant supplementation on micronuclei in subjects with cardiovascular risk. <i>Mutagenesis.</i> 2004 Nov; 19(6): 469-476. PMID: 15548759.</p>	<p>Does not answer the question; about antioxidants.</p>
<p>Stevenson RE, Allen WP, Pai GS, Best R, Seaver LH, Dean J, Thompson S. Decline in prevalence of neural tube defects in a high-risk region of the United States. <i>Pediatrics.</i> 2000 Oct; 106(4): 677-683. PMID: 11015508.</p>	<p>Does not address the question; evaluates the recurrence prevention effort and public awareness campaign of folic acid supplementation for all women of childbearing age.</p>
<p>Suarez L, Hendricks KA, Cooper SP, Sweeney AM, Hardy RJ, Larsen RD. Neural tube defects among Mexican Americans living on the US-Mexico border: effects of folic acid and dietary folate. <i>Am J Epidemiol.</i> 2000 Dec 1; 152(11): 1, 017-1, 023. PMID: 11117610.</p>	<p>Does not measure plasma, RBC or serum folate; about NTD.</p>
<p>Thompson SJ, Torres ME, Stevenson RE, Dean JH, Best RG. Periconceptional multivitamin folic acid use, dietary folate, total folate and risk of neural tube defects in South Carolina. <i>Ann Epidemiol.</i> 2003 Jul; 13(6): 412-418. PMID: 12875798.</p>	<p>Does not answer the question; about supplementation treatment.</p>
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